PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 11625PCT dp:ms	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU02/01226**	International Filing Date *(day/month/year)* 30 August 2002	Priority Date *(day/month/year)* 30 August 2001
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] C12N 5/06, 5/08; C12Q 1/68; A61K 38/30; G01N 33/50		
Applicant THE UNIVERSITY OF ADELAIDE et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of **43** sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [X] Certain observations on the international application

Date of submission of the demand 24 March 2003	Date of completion of the report 12 December 2003
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **TERRY MOORE** Telephone No. (02) 6283 2632

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU02/01226

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages , as originally filed,
pages , filed with the demand,
pages **1-27,** received on **10 December 2003** with the letter of **9 December 2003**

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **28-30,** received on **12 December 2003** with the letter of **9 December 2003**

☒ the drawings, pages , as originally filed,
pages , filed with the demand,
pages **1-13,** received on **10 December 2003** with the letter of **9 December 2003**

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box I5

Amended claims 12 and 13 in part are considered to go beyond the disclosure in the specification as filed. The specification as filed discusses the diagnostic use of IGF-II and the recognition that variation in the capacity of the placenta to produce IGF-II allows predictions to be made concerning the differentiation/migration behaviours of cytotrophoblasts. As such the specification discloses methods of determining the ability of cytotrophoblasts to migrate or differentiate, characterised by measurement of levels of IGF-II or IGF-II coding sequences or characterisation of the capacity of the placenta to produce IGF II. In particular the specification discloses characterisation of INS-VNTR sequences located near the IGF-II gene (see page 6, lines 21-29 and page 13). However amended claims 12 and 13 go beyond a disclosure of IGF-II, TGF beta, CIM6P and INS-VNTR sequences or peptides. The claims recite any sequence associated with regulation of the competition between IGF-II and TGF-beta for binding to CIM6P (claim 11) and specific genes including urokinase plasminogen activator, urokinase plasminogen activator receptor, CIM6P, TGF-beta and plasminogen. As such the claims include genes that are involved in processes that are quite distinct from processes associated with placental IGF-II production.

Rule 67 lists the subject matter which under Article 34(4)(a)(i) an international preliminary examination is not required to be carried out. At item (iv) it specifies methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, as such matter. However the agreement between WIPO and Australia further qualifies this by excepting from exclusion any subject matter which is examined under national grant procedures. Claims 1-8 and 12-17 have nonetheless been considered because the identified subject matter does not contravene Australian law.

Furthermore, it is noted that claims 2 and 7 may include within their scope methods relating to the generation of human beings. Such methods may represent unpatentable subject matter in certain patent countries.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-17	YES
	Claims		NO
Inventive step (IS)	Claims	1-17	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-17	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The invention described in the specification resides in the discovery that IGF-II and TGF-beta compete for binding to the CIM6P receptor in cytotrophoblasts. Upregulation of IGF-II prevents latent TGF-beta binding to the CIM6P receptor and maintains the migratory behaviour of cytotrophoblasts. Downregulation of IGF-II allows latent TGF-beta to bind to CIM6P thereby stimulating cytotrophoblast differentiation and inhibiting migratory behaviour. This discovery can be exploited to regulate cytotrophoblast differentiation and migratory behaviour, particularly in respect of regulating placentation, embryo development and stem cell differentiation and for assessing cytotrophoblast behaviour and pregnancy outcomes.

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 McKinnon et al (2001) J Clin Endocrin Metabol
D2 Hamilton et al (1998) Exp Cell Res
D3 Irving et al (1995) Exp Cell Res
D4 Patent Abstracts of Japan 06-038742
D5 Takahashi et al (1995) J Vet Med Sci
D6 Zhou et al (1992) Endocrinolgy

Novelty and Inventive Step

D1 discloses that the addition of IGF-II to cytotrophoblasts stimulates migration and that migratory activity can be blocked using anti CIM6P antibodies that block the IGF-II-CIM6P (IGFBP2) interaction.

D2 and D3 disclose the addition of IGF-II to cytotrophoblast cultures to stimulate the migratory and invasive behaviour of the cells and to prevent their differentiation into non-migratory cells.

D4 and D5 disclose the use of IGF-II to regulate the culture and differentiation of embryonic stem cells and to obtain precursor pluripotent stem cell lines.

Although all of D1-D5 recognise that IGF-II plays an important role in regulating the migration and differentiation of cytotrophoblasts and placenta formation, with D1 in particular disclosing that this occurs as a consequence of IGF-II binding to CIM6P, none of the citations recognise that this occurs because IGF-II and TGF-beta compete for binding to CIM6P. As such none of the citations disclose or teach toward methods directed at modifying the competition between IGF-II and TGF-beta to promote or inhibit IGF-II binding to CIM6P.

Continued in supplemental box.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of box V2

D6 represents a study of the actions of IGF-II in placental development and its association with the IGFBP2 (CIM6P) receptor. However it does not suggest or teach toward the interactions between CIM6P, IGF-II and TGF-beta. As such it does not clearly teach toward, or disclose the subject matter of the claims.

None of the citations disclose or teach toward methods of diagnosing the predisposition of cytotrophoblast cells to differentiate or migrate, comprising assessing levels of expression of IGF-II or INS-VNTR. As such none of the citations disclose or teach toward the methods of claims 12 and 13 in part, or 14-17 in full.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 12 and 13 are not supported by the description as discussed in the supplemental box relating to I(5).

Claims 10 and 11 lack clarity. The claims recite methods of producing differentiation, division or migration characterised by regulating IGF-II and TGF-beta competition for CIM6P binding by increasing or reducing levels of IGF-II, however they do not define how levels of IGF-II are increased or reduced. Although, from a reading of the specification, it appears that IGF-II levels may be altered by administration of IGF-II, IGF-II analogues, anti-IGF-II antibodies, TGF-beta, TGF- beta analogues or anti-TGF-beta antibodies, these features, or any other ways in which IGF-II levels are altered, are absent from the claims. As such the scope of the claims is unclear.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
11625PCT ms		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/AU02/01226	30 August 2002	30 August 2001

Applicant

THE UNIVERSITY OF ADELAIDE et al

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readable form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (See Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure

   [ ] because this figure better characterizes the invention

   [X] None of the figures

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU02/01226

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C12N 5/06, 5/08; C12Q 1/68; A61K 38/30; G01N 33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
WPIDS, CA: SEE ELECTRONIC DATABASE BOX BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
MEDLINE: SEE ELECTRONIC DATABASE BOX BELOW

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA, WPIDS, MEDLINE: IGF-II, cytotrophoblast, trophoblast, stem cell, IGFBP2, CIM6P, differentiate, migrate, implant, invade, tandem repeat

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	McKinnon T et al "Stimulation of human extravillous trophoblast migration by IGF-II is mediated by IGF type 2 receptor involving inhibitory G protein(s) and phosphorylation of MAPK" **J Clinical Endocrinology & Metabolism** (2001) 86(8), pages 3665-74 See whole document.	1-4, 8, 10-14
X	Hamilton GS et al "Autocrine-paracrine regulation of human trophoblast invasiveness by insulin-like growth factor (IGF)-II and IGF-binding protein (IGFBP)-1" **Exp Cell Res** (1998) 244, pages 147-56 See whole document	1-4, 12, 14

[X] Further documents are listed in the continuation of Box C [ ] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2002	25 OCT 2002
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**TERRY MOORE** Telephone No : (02) 6283 2632

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU02/01226

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Irving JA et al "Functional role of cell surface integrins on human trophoblast cell migration: regulation by TGF-β, IGF-II and IGFBP-1" **Exp Cell Res** (1995) 217, pages 419-27	
X	See whole document	1-4, 12, 14
	Patent Abstracts of Japan 06-038742	
X	JP 04-083866 (N T SCI:KK) 15 February 1994	1-5, 12, 14
	Takahashi A et al "Synergistic effects of insulin-like growth factor II (IGF-II) with leukemia inhibiting factor (LIF) on establishment of rat pluripotential cell lines" **J Vet Med Sci** (1995) 57(3), pages 553-6	
X	See whole document	1-5, 12, 14
	Zhou J et al "Insulin-like growth factor-II and its binding proteins in placental development" **Endocrinology** (1992) 131(3), pages 1230-40	
A	See whole document	All claims